Supporting Statement Part A

The Study to Explore Early Development, Teen Follow-Up Study (SEED Teen)

OMB #

New

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- **Goal of the study:** The purpose of the Study to Explore Early Development, Teen Follow-up Study (SEED Teen) is to assess the health and functioning in a cohort of teens with autism spectrum disorder (ASD) and other developmental disabilities (DDs) who previously participated in an autism research study when they were young. The study will also assess family impacts associated with ASD and other DDs, and service needs and use associated with having ASD and other DDs during the early teen years.

- **Intended use of the resulting data:** Data from SEED Teen will enable investigators to increase scientific understanding of the developmental trajectory and health consequences of ASD among adolescents and enable federal, state, and local governments and organizations to better understand the needs of adolescents with ASD.

- **Methods to be used to collect:** SEED Teen is a follow-up study of children who participated in the SEED case-control study in 2007-2011 when they were 2 to 5 years of age. Mothers or other primary caregivers who participated in the case-control study will be re-contacted when their child is 13-17 years of age and asked to complete two self-administered questionnaires about their child's health, development, education, and current functioning.

- **The subpopulation to be studied:** The initial phase of SEED Teen, which will include children born between 2003 and 2007 and their parent respondents. Children will be identified from four SEED sites in Georgia, Maryland, North Carolina, and Pennsylvania. Three groups of children will be included: children with ASD, children with other (non-ASD) developmental conditions (DD comparison group), and children from the general population who were initially sampled from birth records (POP comparison group).

- **How data will be analyzed:** Health, health care, and developmental outcomes and indicators will be compared in children with ASD, children with other DDs and children in the POP group. Prevalence estimates and 95% confidences intervals for various health and development indicators will be calculated for each group, for select ASD subgroups (defined by severity of symptoms), and for important demographic subgroups. Multivariable log-binomial regression will be used to determine risk factors for given health outcomes and to compare study groups on various indicators. Using chi-square tests, prevalence estimates will also be compared to those from national publicly available population-based surveys.

Supporting Statement Part A.

A. Justification

Section A.1. Circumstances Making the Collection of Information Necessary

This Information Collection Request is submitted under the classification "New" request. The length of data collection requested for Office of Management and Budget (OMB) approval is 3 years. The National Center on Birth Defects and Developmental Disabilities (NCBDDD) at the Centers for Disease Control and Prevention (CDC) is making this request as authorized by Section 301(a)[42 U.S.C. Section 241(a)] and 317(c) of the Public Health Service Act [42 U.S.C. 247b-4], as amended **(Attachment 1.a.)**; the Combating Autism Act of 2006, Pub. Law No. 109-416 **(Attachment 1.b.);** and the Children's Health Care Act of 2000 **(Attachment 1.c.)**.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction and communication and stereotyped behaviors and interests. The U.S. prevalence of ASD is estimated at 1% to 2% (1-3). In addition to the profound, lifelong impacts on individuals' functioning given the core deficits in social-communication abilities, a high proportion of children with ASD also have one or more other developmental impairments such as intellectual disability or attention-deficit-hyperactivity-disorder (3-5) and children with ASDs have higher than expected prevalences of health conditions such as obesity, asthma and respiratory disorders, eczema and skin allergies, migraine headaches, and gastrointestinal symptoms and disorders (4,6).

The Children's Health Care Act of 2000 mandated CDC to establish autism surveillance and research programs to address the number, incidence, correlates, and causes of autism and related developmental disabilities (DDs). Under the provisions of this act, NCBDDD funded Centers for Autism and Developmental Research and Epidemiology (CADDRE) to implement

and complete a case-control study, the Study to Explore Early Development (SEED), to collect and report data on risk factors for ASD and health consequences of ASD in young children. To date two phases of data collection for the SEED case-control study have been completed and a third phase will be initiated soon. OMB first approved "The Study to Explore Early Development' (OMB 0920-0741) in October 2007. The second phase of the effort (SEED 2) was inappropriately granted an OMB-PRA clinical research exemption. A third phase of the effort (OMB 0920-1171) was granted approval by OMB under a new ICR in March 2017. All three phases of SEED collected (will collect) detailed information on 1) children's developmental characteristics and health conditions; 2) mother's reproductive and health history with a particular focus on her health and behaviors during her pregnancy with the SEED index (enrolled) child; and 3) family socio-demographics.

Historically, young children have been the focus of ASD research: diagnosis and symptom detection at young ages, prenatal or early-life risk factors, and the effect of early intervention programs. Meanwhile, the number of children diagnosed with ASD each year has steadily increased and, as children age, the prevalence of adults diagnosed with ASD will likewise increase for several decades. Despite this ongoing demographic shift—which some have called "the autism tsunami"—there has been relatively little research on ASD in adolescence and adulthood. For instance, the most recent data from the Interagency Autism Coordinating Committee shows that less than 1% of autism research dollars were focused on adults or "lifespan" issues (7).

While there is research showing that the majority of ASD diagnoses made in early childhood are retained in adolescence (8) with mostly stable in symptom severity (9), there are major gaps in our understanding of the health, functioning, and experiences of adolescents with ASD and other developmental disabilities. Many of these topics are especially relevant to public

health: adolescents and adults with ASD have been shown to have frequent health problems (10), high healthcare utilization and specialized service needs (11), high caregiving burden (12), require substantial supports to perform daily activities (13), are likely to be bullied (14), or isolated from society (15), and are likely to have food allergies (16) or put on restrictive diets of questionable benefit (17). Many of these problems emerge after early childhood, and more studies are needed to estimate the frequency, severity, and predictive factors for these important outcomes in diverse cohorts of individuals with autism and other developmental conditions.

The children and parents previously enrolled in the SEED case-control study represent a unique opportunity to better understand the trajectory of health outcomes in children identified as having ASD at early ages. SEED includes one of the largest cohorts of children assembled with ASD. In 2017, the oldest SEED children (participated in SEED 1) will be adolescents – aged 10 to 14 years. By June, 2021, they will be 14 to 17 years of age. The teen years are an ideal time to begin a follow-up study as there are many gaps in the current scientific literature on the developmental trajectory and health consequences of ASD among adolescents. Moreover, given the wealth of health, developmental, and risk factor data collected on both the children and parents included in the core SEED case-control study, a follow-up study of the children presents unparalleled opportunities to better understand ASD etiologic subgroups, the health and functioning of children with ASD and other DDs from early childhood to adolescence, family impacts associated with ASD and other DDs, and service needs and use associated with ASD and other DDs.

SEED Teen has several strengths that set it apart from most previous studies. First, the original SEED protocol entails very thorough diagnostic protocols and detailed data collection, providing an extremely well-defined cohort for SEED Teen to follow. Second, many of the extant studies recruited participants as adolescents; SEED Teen will prospectively follow

children from approximately age 4 to adolescence. Finally SEED includes children with developmental disabilities without autism, as well as children with ASD and typically developing children. This will allow researchers to develop hypotheses about whether certain outcomes are specific to autism, or whether they are shared by a broad range of developmental conditions. Taken together, these characteristics will allow SEED to make unique contributions to our knowledge about the health and functioning of autism and developmental disabilities in adolescence.

Additionally, a follow-up study of adolescent SEED participants gives investigators an opportunity to incorporate a protocol to remain in contact with the participants and their families into adulthood, and thus possibly extend the current follow-up study into a longer term follow-up of persons with ASD. (We would seek a new OMB-PRA clearance for any such future studies.)

Section A.2. Purpose and Use of Information Collection

I. How this information will be used and for what purpose:

The information collected in SEED Teen will be used to conduct epidemiologic analyses to assess 1) the developmental trajectory of children identified at young ages of having ASD in comparison to children with other non-ASD developmental disabilities (DDs) and children in a general population cohort; 2) the health and functioning of adolescents with ASD and other DDs in comparison to adolescents in a general population cohort; 3) the healthcare utilization and needs of adolescents with ASD and other DDs in comparison to adolescents in a general population cohort; 4) the education attainment and needs of adolescents with ASD and other DDs in comparison to adolescents in the general population; and 5) family impacts associated with having a child with ASD or other DD with the goal of identifying strategies to help meet the unique needs of these families.

In addition to these core objectives, SEED Teen is designed to address two ancillary objectives: 1) request parent/guardian consent and child assent to maintain contact with SEED Teen participants for possible future follow-up studies when they reach adulthood; and 2) request parent/guardian consent and child assent to share genetic data obtained from biosamples collected in the core SEED 1 case-control protocol with two genetic research consortia established and maintained by the National Institutes of Health.

In the years subsequent to the launch of the first phase of the SEED case-control study (SEED 1), genetic research consortia have been established to allow genetic data from various studies of ASDs to be pooled. Because such consortia were not in existence when SEED 1 was planned and implemented, SEED participants were not appropriately consented to allow their genetic data (obtained from biosamples collected during SEED 1) to be shared in this manner. The CDC IRB recently reviewed the SEED 1 consent forms, the current NIH guidance on submitting genetic data into biorepositories, and recent advances in technology that allow for potential identification of individuals based on their genetic data. They determined that the SEED 1 case-control study consents did not sufficiently address the issue of genetic data sharing. SEED Teen will provide an opportunity to obtain consents for genetic data sharing from SEED 1 participants, and thus maximize the use of the SEED biorepository data.

SEED Teen is a follow-up study of children who participated in the SEED 1 case-control study. The protocol for this OMB-PRA clearance request covers the first wave of SEED Teen which includes children from 4 SEED sites – GA, MD, NC, PA --who participated in the SEED 1 case-control study in 2007-2011 when they were 2 to 5 years of age. The purpose of SEED Teen is to collect data on enrolled children's health and development when they are teenagers. Data will be collected from all three groups originally enrolled in the SEED case-control study – ASD cases and DD and POP control groups. Mothers or other primary caregivers of these

children will be asked to complete two self-administered questionnaires (**Attachments 6.c SEED Teen Health and Development Survey and 6.d Social Responsiveness Scale**) about their children's health, development, education, and current functioning. One of the questionnaires also includes questions on the caregiver's demographics, health, and relationship with the child.

The data collected in SEED Teen will be combined with data collected during the original SEED 1 case-control study in 2007-2011. Thus, SEED Teen provides a unique and rich opportunity to examine the health and developmental trajectory from early childhood to adolescence of children in each of the three study groups and how this trajectory might be related to various demographic, maternal pregnancy, and early childhood health and behavioral factors that were collected in the SEED case-control study, 7-13 years earlier.

The findings from analyses of SEED Teen data will be published in peer-reviewed journals and presented at national scientific and public health meetings and at local community meetings at each site. CDC will also prepare summaries of key findings from these studies written in plain language so as to be accessible to the general public and include them on the CDC website. Webinars and reports detailing SEED Teen findings will also be prepared for partner organizations and stakeholders. The personally identifying information collected will only be used to maintain contact with the participants throughout the course of the study and (if the participant consents), this information may be retained for future contact for a follow-up study.

II. Justification for data collection in terms of positive needs and the negative consequences of not having the information:

With the information collected in this survey, the CDC, along with its partners, will have information on health and development among a U.S. group of adolescents with and without

ASD and other DDs, including adolescents from diverse population subgroups. This information may help inform local, state, and federal resource allocation for services targeting U.S. adolescents and adults with ASD. Additionally, clinicians may find the results useful. Without the information, SEED will not be able to fulfill the originally envisioned purpose for this study, which are part of the larger governmental response to ASD.

CDC's work on population-based ASD studies including SEED Teen contribute key data to inform the Departmental priorities for ASD research, surveillance and services through the Interagency Autism Coordinating Committee (IACC). IACC is a Federal advisory committee that coordinates all efforts within the Department of Health and Human Services (HHS) concerning ASD. One responsibility of the IACC is the development of a strategic plan for ASD research. The *IACC Strategic Plan*, first issued in 2009, is periodically updated through work groups, composed of federal officials and public stakeholders, with extensive input from researchers, adults on the autism spectrum, parents, advocates, and the general public. The *IACC Strategic Plan* is organized around seven general topic areas. The data obtained from SEED Teen will help inform four of the seven topic areas:

- ***What causes ASD, and can disabling aspects of ASD be prevented or preempted?***
- ***What kinds of services and supports are needed to maximize quality of life for people on the autism spectrum?***
- ***How can we meet the needs of people with ASD as they progress into and through adulthood (or across the lifespan)?***
- ***How do we continue to build, expand, and enhance the infrastructure system to meet the needs of the ASD community?***

SEED Teen is especially unique in comparison to other ASD studies in that the information collected in the original case-control study when children were 3-5 years of age will be able to be linked with the data collected in SEED Teen. Thus, SEED Teen will allow for assessments of

how early maternal and child risk factors and child health outcomes potentially influence the trajectory of ASD symptomatology, health outcomes, healthcare needs, and access to healthcare and education services.

Section A.3. Use of Improved Information Technology and Burden Reduction

In order to comply with all legal requirements for privacy of data and consent to participation, all SEED families eligible for participation in SEED Teen will be invited to participate and consent to study participation in a manner that respects the terms and conditions of SORN 09-20-0136, Epidemiologic Studies and Surveillance of Disease Problems, HHS/CCC/NCID and the Data Privacy Act of 1974.

SEED Teen will apply information technology to assure both the quality of the collected data and the privacy and security of the collected data.

All SEED families eligible for participation in SEED Teen will receive an invitation letter (**Attachment 3.a**) briefly describing the study, followed by an introductory phone call. These letters and phone calls will be addressed to the parent or other primary caregiver who completed data collection activities for the SEED case-control study. An electronic, centralized secure SEED tracking system which was established for the case-control study will allow study staff to efficiently locate the correct person and update contact information as needed. This system will also allow SEED staff to personalize the SEED Teen invitation letters. Parents/caregivers who provide verbal consent to enroll in SEED Teen will receive a data collection packet mailing that includes two questionnaires (SEED Teen Health and Development Survey [**Attachment 6.c**] and the Social Responsiveness Scale [**Attachment 6.d**]), and two consent forms (Consent Form for Future Contact [**Attachment 7.a**] and Consent Form for Genetic Data Sharing [**Attachment 7.b**]). They will be asked to complete the questionnaires and consent forms and return them in a pre-paid envelope. Telephone support will also be available to those participants requiring

assistance completing any or all portions of the questionnaires. SEED staff will proactively follow-up with all participants after the data collection mailing is sent to ensure they received the mailing, answer any questions, and offer assistance. Web data collection is not feasible for this first phase of the study due to the study's necessary yet stringent timeline to begin enrollment by 2018 and complete enrollment by 2021 -- given children's dates of birth (i.e. to ensure that all participants will be enrolled when the child is 13-17 years of age); the CDC funding cycle period for SEED Teen activities; and the estimated time to trace and contact all SEED participants potentially eligible for SEED Teen. Development of web-based data collection option with inclusion of all CDC-required security features and testing requirements will be considered for future phases of SEED Teen.

NCBDDD has funded a Data Coordinating Center (DCC) at Michigan State University through a separate contract. The DCC will be responsible for the information technology aspects of the study. This DCC is the same as that previously and currently funded by CDC for the SEED case-control study. For SEED Teen, DCC will develop and manage a secure, CDC-approved, web-based centralized participant tracking system which incorporates select information from the SEED case-control tracking system. The DCC will also develop a secure data entry system with full quality control checks including duplicate data entry functionality. Upon completion of data collection activities, the DCC will export the SEED Teen data into analytic files and will add these data files to a secure CDC-approved remove data access (RDA) server that they maintain. Thus, the DCC is already broadly engaged in SEED activities and maintains all of the key data from the SEED case-control study that will eventually be linked to data collected in SEED Teen.

The DCC has previously created and hosted a custom web-based information system, CIS, which is used for the SEED case-control study. DCC is currently developing plans for the

SEED Teen system which may be developed as a module to CIS or as a separate standalone system. Whichever option is chosen, DCC will include all of the functionality and security features that are currently included in the CIS. CIS was carefully designed to directly support all of SEED data collection workflows, data quality assurance processes, and provide secure database and Internet transaction services. Relevant services provided by CIS for the SEED case-control study include:

- Generation of customized task lists specific to the role of each authenticated user
- Role-based security that restricts user access privileges to the minimum required
- Automated tracking of participant progress
- Generation of bar code labels to identify all study documents.
- Double data entry for data collected on paper forms
- Support for data entry and coding of copyrighted assessment instruments (such as the SRS)
- Ongoing data quality assurance checks
- Automated tracking and quality assurance reports
- Comprehensive audit logging functions
- User support services

Upon completion of data collection activities, the DCC works with the CDC to organize the preparation of pooled analytic data files from the data entered into CIS. This process includes quality control checks of the data collected in CIS before its exported into analytic files; quality control of the export process itself; and de-identification of analytic files by applying a date shifting algorithm previously developed and tested by DCC and removing open string text field data elements that are inherently or likely identifiable (these issues are unlikely to apply to SEED Teen as neither dates nor inherently identifiable text data will be collected and entered from either instrument).

Upon completion of the export and QC process, DCC uploads the analytic data files and accompanying data dictionaries and other documentation onto a remote data access server

(RDA) for access by the site investigators. The RDA meets CDC security requirements and is located in a HIPAA-compliant data-center with full redundant power and security measures.

Summary of Participant Burden Reduction

The web-based information system developed by the DCC will include technology to de-duplicate tracking lists and conduct tracing to ensure that participants do not receive multiple invitation letters. In addition, the system will allow for personalization of invitation mailings and will facilitate data entry for the SEED Teen Health and Development survey (**Attachment 6.c**) and the Social Responsiveness Scale (**Attachment 6.d**). Electronic duplicate data entry systems will be used to reduce data entry errors. While this does not reduce participant burden per se, it does ensure that the data participants took time to provide to this study are prepared in electronic data files in a manner that maximizes data quality.

Section A.4. Efforts to Identify Duplication and Use of Similar Information

SEED Teen is a large and diverse prospective cohort of U.S. children with ASD, other DDs, and typical development that focuses on the health, functioning, and family situation of these adolescents. SEED Teen participants previously underwent rigorous developmental assessments during their participation in the SEED case-control study and contributed rich data concerning maternal pregnancy history, family health history and child early life events. This comprehensive data collection will place SEED Teen in the unique position to study risks and protective factors that predict important outcomes over the life span.

We searched for similar studies with potentially overlapping goals. We included studies that are well-known to researchers in the field and performed supplementary literature searches on PubMed and Google Scholar. In addition, NIH Reporter returned 66 results for “autism” and “adolescence;” most studies were exclusively interested in biological correlates of autism symptoms. The most recent IACC research portfolio for question 6, “What does the future hold,

especially for adults," returned 34 studies. Of the 34, three relevant studies utilized data from the National Longitudinal Transition Survey-2 (NLTS-2), and one additional study (Longitudinal Studies of Autism Spectrum Disorder: 2-23) was included in our review and comparison. Table 1 summarizes the relevant studies that we identified and compares the characteristics of each study to SEED TEEN.

There are two large national surveys (Reference A in Table 1) that collect information about child health and development including teenagers. It is possible to assess children with ASD and other disabilities in these surveys. However, these surveys are cross-sectional only and thus do not allow for in-depth developmental assessments nor for an assessment of the developmental and health trajectory that SEED Teen is designed to include. Moreover, even though the total sample size is large in many of these surveys, because they are designed to cover the entire population of non-institutionalized children 0-17 years of age, the sample sizes for teenagers with specific developmental disabilities such as ASD are small. Also, SEED Teen is specifically designed to address research questions that are most relevant to children with ASD and other DDs. National surveys have a much broader focus and thus, data collection on any specific topic is often much less detailed than SEED Teen. Finally, unlike national surveys, SEED Teen also follows children for whom we already have a wealth of preconception, prenatal, and early post-natal risk factor data which are not available for cross-sectional studies.

The Interactive Autism Network (Reference B in Table 1) is another large survey composed of individuals with autism, but is also cross-sectional and does not have the purposeful sampling and design of the national surveys. This data collection system also is limited in that it does not include a control group of individuals without ASD.

The NLTS-2 (Reference C in Table 1) is a national survey of adolescents in special education designed to study service use and ongoing educational attainment and employment in

this group. Participants were first enrolled in the study during adolescence, so NLTS-2 cannot address how early risk factors impact the long term developmental outcomes of children with and without ASD. Furthermore, because the NLTS-2 is composed entirely of adolescents receiving special education, it does not include a non-disability comparison group.

Other well-established follow-up research studies (References D, E, F in Table 1) also typically begin following individuals during adolescence or adulthood, which limits the ability to explore early-life contributions to later outcomes. And as with IAN and NLTS-2, these studies also lack non-autism comparison groups.

Finally, there are a few longitudinal autism studies that begin in childhood, but these clinic-based studies are much smaller in size than SEED Teen, have limited (or no) comparison groups, and are often focused on autism symptomatology and psychometric evaluation rather than on health, family, and functioning. Further, these studies do not match the depth of SEED Teen's prospectively-collected information in early childhood.

By building upon the already-completed waves of SEED, SEED Teen represents an extremely efficient use of resources – the cost to perform the follow-up components of SEED Teen is much less than the initial, intensive data collection. Thus, SEED Teen is not only a unique source of information about autism and other developmental disabilities, it is further enhancing the value of the existing SEED data.

Table 1. Characteristics of relevant autism studies compared to SEED Teen

Feature	SEED TEEN	Natl Surveys, such as NHIS NSCH (A)	IAN (B)	NLTS 2 (C)	Adolescents and adults with autism (D)	UNC TEACCH (E)	Vanderbilt (F)	Lord Transition (G)	Lord Longitudinal (H)
Follow-up Study Component	Yes			Yes	Yes	Yes	Yes	Yes	Yes
Purposeful recruiting/sampling for racial and socio-economic diversity	Yes	Yes	Yes	Yes	?	?	?	?	?

Purposeful probability – based methods to identify study participants for recruitment	Yes	Yes							
Major focus on child health, daily-life functioning, and family impact	Yes	Yes	Yes	Partial	Yes	Yes			
Large sample size of teen-aged individuals with ASD	Yes			Yes			Yes		
Inclusion of comparison group of teenagers with other (non-ASD) disabilities	Yes	Yes		Yes	Yes				Yes
Inclusion of general population comparison group (teenagers without ASD or other disabilities)	Yes	Yes							
Detailed data available from prospective, developmental assessments conducted in early childhood	Yes								Partial
Detailed data available from early child health outcomes	Yes								
Detailed data available about maternal pregnancy and health risk factors	Yes								
Detailed data available about family health history	Yes								

Links to other studies:
A – National Health Interview Survey: https://www.cdc.gov/nchs/nhis/ and National Survey of Children's Health: http://www.childhealthdata.org/learn/NSCH
B- Interactive Autism Network: https://iancommunity.org/
C – National Longitudinal Transition Survey -2 https://ies.ed.gov/ncser/projects/nlts2/
D- Adolescents and Adults with Autism: http://www.waisman.wisc.edu/family/study_autism.html
E – TEACCH Understanding Autism in Adulthood Research Study: https://www.teacch.com/research/understanding-autism-in-adulthood-research-study
F – Improving Transition for Youth with Autism: http://vkc.mc.vanderbilt.edu/notables/2015/03/improving-transition-for-youth-with-autism/
G – TRANSITIONING TO ADULTHOOD: A PROSPECTIVE LONGITUDINAL STUDY https://projectreporter.nih.gov/project_info_description.cfm?aid=9131788&icde=32880793
H- LONGITUDINAL STUDIES OF AUTISM SPECTRUM DISORDERS: 2 TO 23Awardee Organization: WEILL MEDICAL COLL OF CORNELL UNIV -https://projectreporter.nih.gov/project_info_description.cfm?aid=8268499&icde=6662910

Section A.5. Impact on Small Businesses or Other Small Entities

This data collection will not involve small businesses.

Section A.6. Consequences of Collecting the Information Less Frequently

The information collected from each SEED Teen participant will only be collected once and has not been collected previously.

There are no legal obstacles to reduce the burden.

Section A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

This request fully complies with the regulation of 5 CFR 1320.5.

Section A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A 60-day Federal Register Notice was published in the Federal Registry on May 1, 2017, vol. 82, No. 82, pp 20343 **(Attachment 2).** CDC did not receive public comments related to this notice.

Prior to developing the funding announcement for SEED Teen, CDC discussed the possibility of a follow-up study with external partners through several settings:

- NCBDDD holds meetings and conference calls with partners to provide updates on Center activities and to solicit input and comments. For the past 7 years, we have received numerous ad hoc comments from partners that the SEED project represents an unparalleled opportunity to understand the long term trajectory of children with ASD.
- The PIs and other investigators at the extramural SEED sites have repeatedly encouraged CDC and other government funding organizations such as NIH and HRSA to consider funding a long term follow-up study of SEED participants.
- In January, 2015, CDC convened an external peer review panel to review autism research activities in NCBDDD with a focus on SEED. As part of this review the panel was asked to make recommendations about future SEED projects including the possibility of a follow-up of children enrolled in the SEED case-control study.
    - External Peer Review Panel Members were: Alison Singer, MBA, Autism Science Foundation; Stephen Buka, ScD, Harvard University; Chris Gunter, PhD, Marcus Autism Center, Children's Healthcare of Atlanta, and Emory University School of Medicine; Alycia Halladay, PhD, Autism Science Foundation, Susan L Hyman, MD, University of Rochester School of Medicine; Michael Kogan, PhD, Health Resources and Services Administration; Matthew Longnecker MD, ScD, National Institute of Environmental Health Sciences; and Jennifer Mulle, PhD, Emory Rollins School of Public Health.
    - The panel reported that SEED could make a unique contribution to our understanding of autism in the areas of longitudinal documentation of symptoms within biologic and clinical phenotypes, and in understanding the impact of interventions.

- They recommended the study include data collection within the several research domains: course of medical and behavioral symptoms associated with ASD: current functioning of children related to health/wellness, behavior, language, education, social and community challenges; current diagnoses, symptoms and course relative to diagnosis and treatment of comorbid medical and psychiatric conditions; relationship of the use of health and educational services relative to trajectory/outcome; and broader family functioning including impact on caregiver and sibling health, stress, and finances
- They additionally identified several specific research topics they felt particularly important to include in a follow up study -- obesity, elopement & accidents, bullying, social and community program impact, quality of life as an outcome measurement and access to care/medical home participation.

CDC carefully considered these recommendations in designing SEED Teen. SEED Teen will collect detailed data within each of the research domains and specific topic areas recommended by the peer-reviewed panel.

During the process of developing the SEED Teen protocol, CDC consulted a number of persons outside CDC and researched previous studies to ensure that this data collection is not duplicative and that the study design, data elements, and instruments are appropriate.

Finally, the principal investigators (PIs) at four of the SEED 1 case-control study sites played an integral role in the design and the development of SEED Teen. The SEED Teen protocol development was a collaborative effort between the CDC, NCBDDD and one funded extramural SEED Center, the University of North Carolina at Chapel Hill (UNC). Additionally, UNC has partnered with two other sites that participated in SEED 1 case-control study (Johns Hopkins University and University of Pennsylvania). Under agreements with these two institutions, UNC will collect data from SEED 1 participants from the Maryland SEED site and Pennsylvania SEED site in addition to the North Carolina SEED site. CDC worked with individuals from all three sites in developing SEED Teen instruments and protocol.

Section A.9. Explanation of Any Payment or Gift to Respondents

Respondents will receive a $30 cash card with a thank you letter (**Attachment 8**) as a token of appreciation. The CDC IRB approval of the study (**Attachment 10)** included the review

and approval of this type of gift. Incentives are provided to parents who are the respondents in this study. No additional incentives are provided to the teens themselves.

All SEED parents cope with challenges above and beyond what parents of typically developing children face. Use of a nominal incentive will be one important means of motivating invited caregivers to participate in SEED Teen and thus, the incentive is critical to helping us achieve high response rates. Parents and other primary caregivers who participated in the SEED case-control study cited altruistic reasons when asked why they chose to participate; however, many participants also noted that a primary barrier to study completion was the difficulty in finding sufficient periods of uninterrupted time needed to complete study instruments. This problem was often exacerbated for many participants of lower socioeconomic status (SES) – groups SEED was specifically designed to include.

Providing a nominal monetary incentives of $30 in SEED Teen will allow parents to offset other competing personal demands such as caregiving or meal preparation. Given the diversity of our study population, we also need to be mindful that some participants have low literacy level and thus need more support from SEED staff, for example help completing their data collection instruments over the phone rather than using the self-administered mode. This will take longer and thus add burden to these participants. This could be particularly problematic because these participants might have the greatest personal time constraints and/or might not have resources to pay for extra child care or meals out such that they can offset the demands of completing SEED Teen study instruments.

Section A.10. Protection of the Privacy and Confidentiality of Information Provided by Respondents

This submission has been reviewed by the NCBDDD Information Systems Security Officer and the CDC Chief Privacy Officer and determined that the Privacy Act does apply

because a system of records will be maintained by CDC, a federal agency, that includes information on individuals, including but not limited to medical history, and an identifying number assigned to each individual. Personally identifiable information will be collected and maintained under Privacy Act System of Records 09-20-0136, "Epidemiologic Studies and Surveillance of Disease Problems." Analytic datasets transmitted to CDC by the DCC will be encrypted. The data collected is jointly owned by the CDC and the participating research sites. All employees at all SEED sites associated with this project, including contractors, will sign a non-disclosure agreement.

Verbal consent for participation in SEED Teen will be obtained during the invitation call before sending participants the data collection packet. Additionally, the participant information sheet included in the data collection packet provides a full description of participants' rights in any easy to read Frequently Asked Questions format (**Attachment 6.b**). These questions cover all relevant areas included in study consent forms: study purpose, description of study tasks, potential risks and benefits to participant, monetary incentives, safeguards taken to protect participant privacy, data sharing, and explicit language that participation in SEED Teen is voluntary. Specifically, the following language is included in the information sheet:

- "Your decision to be in the study is up to you. Your participation is voluntary. There is no penalty if you do not want to be in the study. We will not discuss your decision to participate or not participate in SEED with anyone outside the study."
- "All answers that you give will be kept private. Because sensitive information is collected in this study, *<site>* received a 'Certificate of Confidentiality.' This means that any information that *<site>* has that identifies you or your child will be used only for this project. It cannot be given to anyone else unless you give your written consent. But under law, we may report to the state if you tell us you are planning to cause serious harm to yourself or others."

Finally, the participant's action to complete and return the data collection forms to the SEED site, or to request assistance to complete the study instruments over the phone with SEED staff, constitutes implied consent.

The consent forms for future contact (**Attachment 7.a**) and genetic data sharing (**Attachment 7.b**) will be included in the Data Collection packet; however, during the invitation call staff will make clear that these forms are supplemental rather than a core part of SEED Teen. This messaging is also provided in the written information sheet that is provided in the data collection packet (**Attachment 6.b).**

While we will encourage participants to complete and return both consent forms, we have taken steps to ensure participants understand that a decision to not consent to either future contact or genetic data sharing will in no way impact their eligibility or participation in SEED Teen.

All data on individuals participating in SEED Teen will remain confidential at all times. Due to the sensitive nature of certain data collection components, a consolidated application for 301(d) Certificates of Confidentiality for the two sites conducting SEED Teen (North Carolina SEED and Georgia SEED) was requested and has been awarded. The SEED Teen instruments include sensitive information which parents might be reluctant to share without assurance that all available protections to maintain the privacy of their information are being taken. Additionally, analytic data files for SEED Teen will eventually be linked to those from the SEED case-control study. A Federal Certificate of Confidentiality affords the study and the participant additional protection from involuntary disclosure of information collected in the study. The exposure of the identity of study participants will be avoided.

A 12-digit identification number will be employed to encode the participant identity on data collection forms. The linkage of the identification number and the participant personal

identifiers will be provided by the participant tracking system for this study (see below). All efforts will be taken to ensure that all proposed research methods comply with human subjects' requirements. The DCC will develop a participant tracking and data entry system for SEED Teen that complies with all current (and future) CDC security requirements for such web-based applications and is located in a HIPAA-compliant data-center with full redundant power and security measures.

The risks to study participants are expected to be minimal. Provisions for protecting privacy and confidentiality of study subjects will be strictly maintained. Study results will always be presented in aggregate form, thereby further preventing identification of individual subjects.

All analytic data files will be shared with SEED Teen investigators through a RDA platform maintained by the DCC with oversight from CDC. Specific personally identifiable information (PII) (such as names, address, phone numbers, etc.) collected as part of the SEED Teen tracking system will not be included in the data files on the RDA. However, the analytic data files will not (and cannot) be considered completely de-identified. SEED Teen data will be maintained in data tables that can be linked to data from the SEED case-control study. The composite SEED and SEED Teen data files will contain more than 20,000 variables per participant. Although the major issues related to identifiability will be addressed, with this volume of data it is not possible to ensure that combination of data about a research participant will not result indirectly, by reference to other information to identification of study participants. Scientists, colleagues, and collaborators who are given access to data from SEED Teen must sign a confidentiality and data use oath that describes how the data should be used and stored. The only currently approved mechanism for SEED Teen data access is through the RDA maintained by the DCC. All analyses are conducted on the RDA and aggregate results are downloaded but

individual-level data are not. DCC actively monitors the RDA and ensures that data are not downloaded. The Principal Investigator of each SEED Teen site has full and direct responsibility for tracking the use of SEED Teen data at their site and assuring that each person who has access to the data has read and signed the confidentiality and data use oath. Each site maintains files of the signed confidentiality and data use oaths. Signed statements will also be kept on file at the CDC. It will be left to the discretion of the individual sites to determine when the statements should be renewed for specific individuals or projects. In keeping with HHS policies for data management of federally-funded studies, NCBDDD will review SEED Teen data elements to determine whether and how select SEED Teen data items may be made available to external researchers through a restricted access mechanism in which the privacy of SEED Teen participants is fully maintained.

Section A. 11 Institutional Review Board Approval and Justification for Sensitive Questions

CDC IRB approval was granted on 3/16/2017 and will expire on 3/15/2018. The current IRB approval letter is included as **Attachment 10**.

SEED Teen was developed by study investigators to collect information to address the following research goals: 1) understand the developmental trajectory of children identified at young ages of having ASD in comparison to children with other non-ASD developmental disabilities (DDs) and children in the general population; 2) understand the health and functioning of adolescents with ASD and other DDs in comparison to adolescents in the general population; 3) understand the healthcare utilization and needs of adolescents with ASD and other DDs in comparison to adolescents in the general population; 4) understand the education attainment and needs of adolescents with ASD and other DDs in comparison to adolescents in the general population; and 5) understand family impacts associated with having a child with

ASD or other DD with the goal of identifying strategies to help meet the unique needs of these families.

Given these research domains, SEED Teen instruments include questions on sensitive topics including children's specific health conditions, details about children's current functioning and diagnosed disabilities, children's need for special services, adverse events in children's lives such as bullying, stressful life events experienced by the child and family, parental expectations for the child's future (which might be a sensitive topic for children in the ASD and DD group particularly), parent's health conditions including diagnosed mental health disorders, parent's relationship with the child, family use of social services such as food stamps, and household income. Parents are told that they may choose to skip any question. In addition, study staff are available to answer any questions and to accommodate participants who prefer to complete the instruments over the phone. We will also hire staff who are sensitive to the well-being of participants who are emotionally vulnerable and also provide training to all staff on how to address sensitive situations that may arise during their contacts with participants.

Section A.12. Estimates of Annualized Burden Hours and Costs

We estimate that 1,410 SEED families are potentially eligible to participate in SEED Teen. The parent or other primary caregiver who acted as the main respondent for the SEED case-control study will be mailed an invitation packet **(Attachment 3)** that includes an invitation letter, response card, and list of ways to contact the study site. Upon agreement to participate in the study, a data collection packet that includes two questionnaires (**Attachment 6.c and 6.d)** and two consent form **(Attachment 7.a and 7.b)** will be mailed to the participants. The questionnaires and consent forms will be conducted one time only.

The a priori SEED Teen study recruitment enrollment and completion targets are as follows. Each site is expected to:

- Successfully trace and contact a minimum of 60% of SEED families who are potentially eligible to participate in SEED Teen.
- Enroll a minimum of 70% of those participants who are successfully contacted and are determined to be eligible for inclusion in SEED Teen.
- Complete data collection activities on 90% of enrolled participants.

1,410 SEED families who participated in SEED 1 are potentially eligible for contact and participation in SEED Teen (see Supporting Statement Part B for a list of eligibility criteria in SEED Teen). We estimate that a minimum of 60% (n=846) of parents/caregivers sent the invitation mailing or will be successfully contacted and participate in the invitation call. We estimate that 80% (n=677) of the families who participate in the invitation call will meet the eligibility criteria for SEED Teen and 70% of those will enroll in SEED Teen – that is 474 parents/caregivers will enroll. We estimate that 90% of enrolled parents/caregivers (n=427) will complete the SEED Teen Health and Development Survey, SRS, and supplementary consent forms. Therefore, the minimum final sample of SEED Teen participants is expected to be: 115 ASD, 164 DD, and 148 POP (427 total participants).

Burden Hours Estimates

Reading the letter and other materials in the invitation mailing will take approximately 5 minutes. Thus, the estimated response burden for the 1,410 potentially-eligible SEED families sent the invitation mailing is 118 hours. As stated above, we estimate that a minimum of 60% (n=846) of parents/caregivers sent the invitation mailing or will be successfully contacted and participate in the invitation call. The estimated response burden for the invitation call is thus 212 hours. We estimate that 80% of the families who participate in the invitation call will meet the eligibility criteria for SEED Teen (see Supporting Statement Part B for a list of eligibility criteria) and 70% of those will enroll in SEED Teen – that is 474 parents/caregivers will enroll. We assume all 474 enrolled families will complete the follow-up call to confirm data collection packet receipt and will review the materials in the data collection packet. Thus, the estimated

response burden for follow-up call and data collection packet review is 119 hours. Finally, we estimate that 90% of enrolled parents/caregivers (n=427) will complete the SEED Teen Health and Development Survey, SRS, and supplementary consent forms. Thus, the estimated response burden is 284 hours for the SEED Teen Health and Development Survey; 142 hours for the SRS and 36 hours for the supplementary consent forms.

The total response annualized burden for all study steps – invitation mailing through completion of supplementary consent forms – is estimated to be 303 hours.

There are no costs to respondents other than their time.

BURDEN TABLE:

A.12.A. Estimated Annualized Burden Hours

Type of Respondents	**Form Name**	**No. of Respondents**	**No. Responses per Respondent**	**Average Burden per Response (in hours)**	**Total Burden Hours**
Eligible families who were enrolled in SEED 1	Invitation Packet **(Attachment 3)**	470	1	5/60	39
Eligible families who were enrolled in SEED 1	Invitation Call Script **(Attachment 4)**	282	1	15/60	71

Families who agreed to participate in SEED Teen	Follow-up Call Checklist **(Attachment 5)**	158	1	10/60	26
Families who agreed to participate in SEED Teen	Data Collection Packet **(Attachment 6)**	158	1	5/60	13
Families who agreed to participate in SEED Teen	SEED Teen Health and Development Survey **(Attachment 6.c)**	142	1	40/60	95
Families who agreed to participate in SEED Teen	Social Responsiveness Scale **(Attachment 6.d)**	142	1	20/60	47
Families who agreed to participate in SEED Teen	Supplemental Consent Forms **(Attachment 7)**	142	1	5/60	12
TOTAL		**1,494**		**100/60**	**303**

The annualized cost burden is shown in Table A.12.B. The median hourly wage rate is based on the most recent (May 2015) National Occupational Employment and Wage Estimates for all occupations, published on the Bureau of Labor Statistics website which is $17.40. See http://www.bls.gov/oes/current/oes_nat.htm.

A.12.B. Estimated Annualized Burden Costs

Type of Respondents	**Form Name**	**Total Burden Hours**	**Hourly Wage Rate ($)**	**Total Respondent Costs ($)**
Eligible families who were enrolled in SEED 1	Invitation Packet **(Attachment 3)**	39	$17.40	$678.60
Eligible families who were enrolled in SEED 1	Invitation Call Script **(Attachment 4)**	71	$17.40	1,235.40
Families who agreed to participate in SEED Teen	Follow-up Call Checklist **(Attachment 5)**	26	$17.40	$452.40

Families who agreed to participate in SEED Teen	Data Collection Packet **(Attachment 6)**	13	$17.40	$226.20
Families who agreed to participate in SEED Teen	SEED Teen Health and Development Survey **(Attachment 6.c)**	95	$17.40	$1,653.00
Families who agreed to participate in SEED Teen	Social Responsiveness Scale **(Attachment 6.d)**	47	$17.40	$817.80
Families who agreed to participate in SEED Teen	Supplemental Consent Forms **(Attachment 7)**	12	$17.40	$208.80
TOTAL		**303**		**$5,272.20**

Section A.13. Estimates of Other Total Annual Cost Burden to Respondents or Record Keepers

There are no costs to respondents associated with either capital and startup efforts or operation and maintenance of services for this project.

Section A.14. Annualized Cost to the Government

The average annualized cost to the Government to collect this information is $697,632.

		Total ($)
Federal Government Personnel costs	SEED Teen Principal Investigator	$40,444
	SEED Teen Project Officer	$28,350
	SEED Teen Data Coordinator	$14,553
	SEED Teen Collaborator	$16,636
	SEED Teen – GA Site Principal Investigator	$29,614
	SEED Teen – GA Site Project Coordinator	$11,975
Contractor and Grantee Costs	Development and maintenance of web-based, centralized participant tracking and data entry system for SEED Teen (DCC contract)	$306,060
	Contractor costs for GA SEED (salaries for recruiter/ interviewer, clinical coordinator, and data analyst; incentives)	$52,742

	Grantee (University of North Carolina at Chapel Hill)	250,000
Total		$697,632

Section A.15. Explanation for Program Changes or Adjustments

This is a new data collection.

Section A.16. Plans for Tabulation and Publication and Project Time Schedule

One to two months after OMB approval, invitation and data collection materials will be mailed by the two SEED Teen sites to eligible individuals.

A. 16. Project Time Schedule	
Activity	**Time Schedule***
Print SEED Teen materials (invitation packet, data collection packet, supplemental consent forms, thank you letter, pre-addressed, stamped envelopes, etc.)	Immediately after OMB approval
Identify and recruit participants – send invitation packet to participants	1-2 months after OMB approval
Data collection begins – send data collection packet to participants	1-2 month after OMB approval
Complete data collection	3 years after OMB approval
Finalize data cleaning and entry	3.5 years after OMB approval

Prepare analytic data files and link data to SEED 1	4 years after OMB approval
Analyze data, draft reports, and present findings	4-5 years after OMB approval

Section A.17. Reason(s) Display of OMB Expiration Date Is Inappropriate

The display of the OMB expiration date is appropriate, no exception is sought.

Section A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

There are no exceptions to the certification.